

**UNITED STATES DISTRICT COURT  
NORTHERN DISTRICT OF OHIO  
EASTERN DIVISION**

**IN RE: NATIONAL PRESCRIPTION  
OPIATE LITIGATION**

THIS DOCUMENT RELATES TO:

*Track Three Cases*

MDL No. 2804

Case No. 1:17-md-2804

Judge Dan Aaron Polster

**REPLY IN SUPPORT OF DEFENDANTS'  
MOTION TO EXCLUDE CERTAIN OPINIONS AND  
TESTIMONY OF DR. KATHERINE KEYES**

**REPLY EXHIBIT 3**

## RESEARCH ARTICLE SUMMARY

## PUBLIC HEALTH

# Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016

Hawre Jalal, Jeanine M. Buchanich, Mark S. Roberts, Lauren C. Balmert, Kun Zhang, Donald S. Burke\*

**INTRODUCTION:** The epidemic of substance use disorders and drug overdose deaths is a growing public health crisis in the United States. Every day, 174 people die from drug overdoses. Currently, opioids (including prescription opioids, heroin, and synthetic opioids such as fentanyl and its chemical analogs) are the leading cause of overdose deaths. The overdose mortality data can reveal the complex and evolving dynamics of drug use in the United States.

**RATIONALE:** Reports on the U.S. drug overdose epidemic tend to focus on changes in yearly statistics. Improved understanding of the long-term dynamics of the overdose epidemic may aid in the development of more effective epidemic prevention and control strategies. At present, there are no reliable methods to forecast the likely future course of the epidemic. We focused on deaths from overdoses as a relatively reliable metric of the epidemic because all deaths are required to be reported in all U.S. states and territories using the standardized International

Classification of Diseases. In an effort to understand the epidemic dynamics and perhaps predict its future course, we analyzed records of 599,255 deaths from 1979 through 2016 from the National Vital Statistics System where unintentional drug poisoning was identified as the main cause of death. We examined the time course of the overall number of deaths; the contributions of individual drugs (prescription opioids, heroin, synthetic opioids like fentanyl, methadone, cocaine, methamphetamine) to the overall curve; changes in the populations most affected by each drug as measured by demographic factors of age, sex, race, and urbanicity; and changes in the geographic distribution of deaths due to each drug as measured by the county of residence of each decedent.

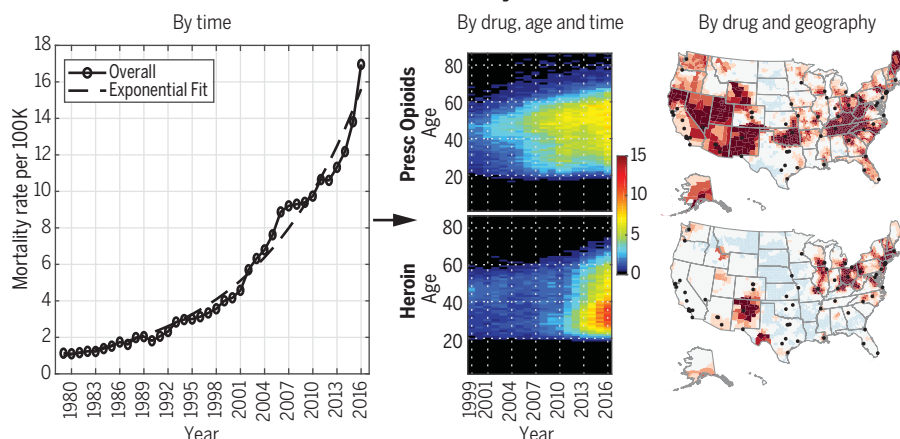
**RESULTS:** The overall mortality rate for unintentional drug poisonings in the United States grew exponentially from 1979 through 2016. This exponentially increasing mortality rate has tracked along a remarkably smooth trajectory (log linear  $R^2 = 0.99$ ) for at least 38 years

(left panel). By contrast, the trajectories of mortality rates from individual drugs have not tracked along exponential trajectories. Cocaine was a leading cause in 2005–2006, which was overtaken successively by prescription opioids, then heroin, and then synthetic opioids such as fentanyl. The demographic patterns of deaths due to each drug have also shown substantial variability over time. Until 2010, most deaths were in 40- to 50-year-old persons, from cocaine and increasingly from prescription drugs. Deaths from heroin and then fentanyl have subsequently predominated, affecting younger persons, ages 20 to 40 (middle panel). Mortality rates for males have exceeded those for females for all drugs. Rates for whites exceeded those for blacks for all opioids, but rates were much greater among blacks for cocaine. Death rates for prescription drugs were greater for rural than urban populations. The geographic patterns of deaths also vary by drug. Prescription opioid deaths are widespread across the United States (right panel), whereas heroin and fentanyl deaths are predominantly located in the northeastern United States and methamphetamine deaths in the southwestern United States. Cocaine deaths tend to be associated with urban centers. The online manuscript provides many details of the patterns of mortality in these data.

**CONCLUSION:** The U.S. drug overdose epidemic has been inexorably tracking along an exponential growth curve since at least 1979. Although there have been transient periods of minor acceleration or deceleration, the overall drug overdose mortality rate has regularly returned to the exponential growth curve. This historical pattern of predictable growth for at least 38 years suggests that the current opioid epidemic may be a more recent manifestation of an ongoing longer-term process. This process may continue along this path for several more years into the future. Paradoxically, there has been substantial variability with which specific drugs have become dominant in varying populations and geographic locales. This variability all but negates the possibility of confident predictions about the future role of specific drugs. Indeed, it is possible that a future overdose epidemic may be driven by a new or obscure drug that is not among the leading causes of drug overdose death today. Understanding the forces that are holding multiple subepidemics together onto a smooth exponential trajectory may be important in revealing, and effectively dealing with, the root causes of the epidemic. ■

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## Overdose Mortality Rate



**Exponential growth in overdose deaths.** The smooth overall U.S. overdose mortality curve (left panel) is a composite of multiple subepidemics, as revealed by changing patterns of overdose deaths by age distribution (middle panel; color indicates deaths per 100,000 persons), and by geography (right panel; color shows hotspots), for prescription opioids (upper) and heroin (lower). Subepidemic patterns for other drugs are shown in the full manuscript.

## RESEARCH ARTICLE

## PUBLIC HEALTH

# Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016

Hawre Jalal<sup>1</sup>, Jeanine M. Buchanich<sup>2</sup>, Mark S. Roberts<sup>1</sup>, Lauren C. Balmert<sup>2,4</sup>, Kun Zhang<sup>5</sup>, Donald S. Burke<sup>3\*</sup>

Better understanding of the dynamics of the current U.S. overdose epidemic may aid in the development of more effective prevention and control strategies. We analyzed records of 599,255 deaths from 1979 through 2016 from the National Vital Statistics System in which accidental drug poisoning was identified as the main cause of death. By examining all available data on accidental poisoning deaths back to 1979 and showing that the overall 38-year curve is exponential, we provide evidence that the current wave of opioid overdose deaths (due to prescription opioids, heroin, and fentanyl) may just be the latest manifestation of a more fundamental longer-term process. The 38+ year smooth exponential curve of total U.S. annual accidental drug poisoning deaths is a composite of multiple distinctive subepidemics of different drugs (primarily prescription opioids, heroin, methadone, synthetic opioids, cocaine, and methamphetamine), each with its own specific demographic and geographic characteristics.

The epidemic of substance use disorders and drug overdose deaths in the United States is a growing public health crisis. Every day, 174 people in the United States die from drug overdoses (1). Currently, opioids (including prescription opioids, heroin, and synthetic opioids such as fentanyl and its chemical analogs) are the main causes of overdose deaths in the United States, leading the U.S. government to declare the opioid crisis to be a public health emergency (2).

Knowledge of the opioid epidemic has been mostly limited to scattered statistics that only reveal selected aspects of the epidemic, such as specific geographic regions, specific time periods, and/or specific drugs. For example, a recent National Center for Health Statistics (NCHS) data brief shows that the Appalachian region and southwest region have overdose death rates statistically higher than the national rate (3). Similarly, a recent study has identified geospatial clusters of heroin-related overdose deaths in Southern California in 2000, and emerging later in New England, the Mid-Atlantic, and the Great Lakes region between 2013 and 2014 (4).

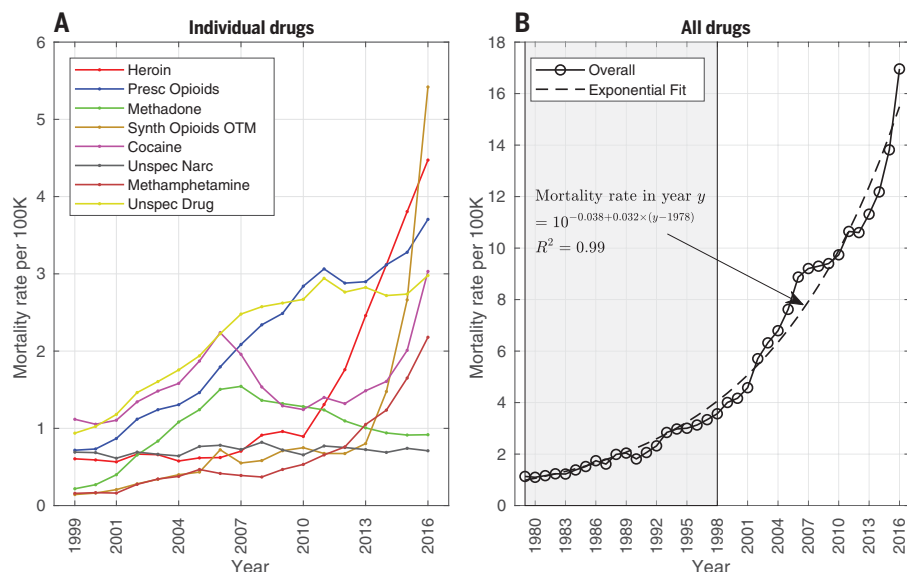
We lack a detailed analysis of the opioid epidemic in the context of the larger drug epidemic that reveals the complex and evolving dynamics of drug use in the United States (5). This manuscript examines mortality patterns of all accidental (unintentional) drug poisonings as reported through the U.S. National Vital Statistics

System from 1979 through 2016. We describe the overall pattern of drug overdose deaths in the United States and reveal specific aspects of these deaths by drug, demography, and geography; we refer to these patterns as subepidemics.

## The overdose epidemic is a composite of multiple subepidemics

Annual mortality rates attributed to prescription opioids, heroin, methadone, synthetic opioids other than methadone, cocaine, methamphetamine, unspecified narcotics, and unspecified drugs are shown in Fig. 1. Drug classes are defined in the supplementary materials and table S1, which sorts the drugs by their International Classification of Diseases (ICD) codes. Accidental drug poisoning trend analyses begin in 1979 with the ninth revision (ICD-9), owing to comparability issues with the cause of death in earlier revisions. Similarly, analyses by drug and drug class begin in 1999 (with ICD-10) because those classifications are not comparable with ICD-9.

Since 2010, the mortality curves for all drug types have been increasing, except for methadone and for unspecified drugs and narcotics. Each drug's mortality curve shows some variability. For example, the mortality rate from prescription opioids decreased slightly in 2012, whereas the mortality rates from heroin and synthetic opioids have been increasing rapidly. These trends may be related because several epidemic interventions may have reduced the impact of prescription opioids around 2010, including the reformulation of OxyContin in 2010 (6), implementation of pain clinic laws and mandatory checking of Prescription Drug Monitoring Program data by prescribers (7), the reduction in



**Fig. 1. Mortality rates from unintentional drug overdoses.** (A and B) Mortality rates for (A) individual drugs and (B) all drugs. Detailed data for individual drugs are only available from 1999 to 2016, although additional data for all drugs are available since 1979 (this area is grayed out). The exponential equation and fit are shown for all drugs. (Synth Opioids OTM: synthetic opioids other than methadone. This category includes fentanyl and its analogs.)

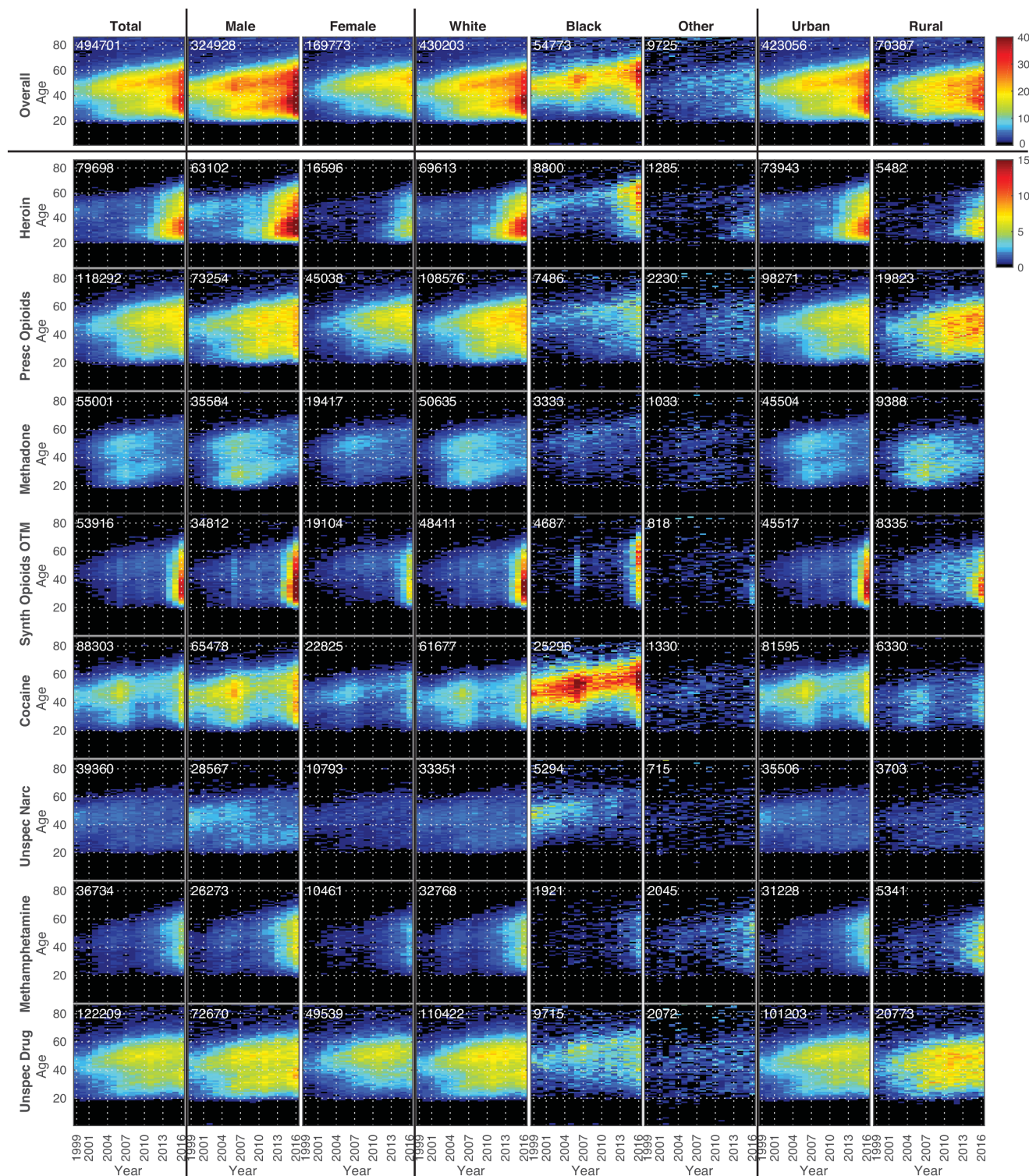
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the amount of opioids prescribed (8), and the rescheduling of hydrocodone compounds in 2014 (9). Although these changes may have reduced the overdose deaths from prescription opioids, it is possible that they may have led some

opioid-dependent persons to switch to illicit opioids, such as heroin and fentanyl (10–12). Economic factors may also have contributed to the transition from prescription opioids to heroin; heroin is increasingly more available, easier to

use through non-oral routes, and becoming purer and less expensive than prescription opioids (13). In addition, the subsequent sharp increase in fentanyl overdose deaths after 2013 is consistent with law enforcement data showing



**Fig. 2. Heatmaps showing the subepidemics by demography and urbanicity.** Total number of deaths in each category from 1999 through 2016 are shown in the upper left corner of each plot. The colors indicate age-adjusted mortality rates per 100,000 people. (Synth Opioids OTM: synthetic opioids other than methadone. This category includes fentanyl and its analogs.)



increased seizures of illicitly manufactured fentanyl (14, 15).

Several other fluctuations observed in the drug-specific mortality curves may also, in retrospect, be explainable. For example, in 2006, a spike in overdose deaths in the United States associated with fentanyl was traced to a production laboratory in Mexico (16). Similarly, the decline in methadone deaths after 2007 may be attributed to the removal of methadone from the preferred drug list by state Medicaid programs, which used to be major sources of methadone prescriptions for pain management (17). The rise and fall of cocaine-related overdose deaths in the United States appears to be linked to production and supply in Colombia, which in turn have reflected diplomatic turns of events in a decades-long civil war (18). Although opioids are the major offenders, drugs other than opioids, such as cocaine and methamphetamine, now also contribute substantially to the rising counts of overdose deaths in the United States (19).

We also examined the mortality rates for deaths reported as being due to unspecified narcotics and unspecified drugs. Mortality rates from the unspecified narcotics have remained stable during the study period, but unspecified drugs closely follow prescription opioid mortality rates until 2008 and start to diverge after 2013, possibly indicating improvements in vital statistics reporting by some states.

Mortality curves from individual drugs do not show regular or predictable growth patterns. Nonetheless, we observed that the annual sum of all drug overdose mortality rates follows a remarkably smooth mathematical trajectory. Figure 1B plots changes in the total accidental poisoning mortality rate, from all drugs. Note that the total mortality rate per year is less than the sum of the mortality rates reported for individual drugs, owing to listing of more than one drug on the death certificate in many individual cases (see fig. S2). The total accidental poisoning mortality rate closely tracks along an exponential growth curve defined as annual overall mortality rate in year ( $y$ ) =  $10^{(a + b*(y - 1978))}$ , where  $a = -0.038$  [confidence interval (CI) = (-0.104, 0.027)] and  $b = 0.032$  [CI = (0.030, 0.034)]. With this exponential growth, the doubling time is approximately 9 years. Of particular interest is the observation that the first half of this long-term smooth exponential growth curve predates the current opioid epidemic.

### The drug-specific subepidemics differ significantly with respect to their time course, geographic spread, and demographic groups affected

Next, we examined death record data available from 1999 to 2016 to determine if there were any patterns in the demography or geography of mortality by drug that might explain how these variable individual drug curves might meld into a single smooth exponential process. To reveal patterns in these data, we use visualization techniques consisting of heat-

maps (Fig. 2) and geospatial hotspot analyses (Fig. 3).

Figure 2 is a matrix of 72 individual age distribution heatmaps depicting how the age of overdose decedents has historically changed over time, as analyzed by drugs, gender, race, and urbanicity. Age has been recognized as an important predictor in transitions from non-use or asymptomatic use to problematic drug use (20, 21) of illicit drugs, and the middle-aged have had higher rates of prescription opioid deaths than other age groups (3, 22–24). In addition, significant increases in heroin overdose-related hospitalizations among the age groups of 20 to 29 and 50 to 59 have recently been identified, suggesting potential new cohorts of heroin users among these age groups (25, 26).

These age distribution heatmaps reveal some distinct patterns. One pattern is a clear bimodal distribution of unintentional drug overdoses: a younger group (age 20 to 40 years) and an older group (age 40 to 60 years). The relative amplitudes of these groupings vary according to drug, gender, race, and urbanicity. The younger age group predominates among deaths due to heroin and synthetic opioids, and especially among males, whites, and in urban counties. Mortality rates from prescription opioids and unspecified drugs were higher among the older age group, especially among females, among whites, and in rural counties.

Recent studies have examined the unspecified drug overdose death category and attributed some deaths in this category to prescription opioids because many states have drastically under-reported prescription opioid-related overdose deaths, owing to lack of toxicology testing for drug specificity in overdose deaths (27). From 1999 to 2016, there were 112,480 drug overdose deaths in which unspecified drugs were identified as the contributory cause of death, as compared to 106,193 deaths in which prescription opioids were a contributory cause of death. The patterns of overdose mortality rates for which the drug was unspecified closely resemble the patterns for prescription opioids across age, gender, race, and urbanicity. The heatmaps clearly present these similarities.

Mortality differences between male and female rate are associated with age and type of drug. Prior reports of prescription opioid mortality rates have shown nearly four times higher rates in younger males than younger females, in contrast to only 1.3-fold higher rates in older males relative to older females (28). The heatmaps reveal that these differences can be mostly explained by the type of drug. The higher risk among young males relative to young females is mostly attributable to heroin and synthetic drugs, whereas the risk of death among older females is mostly attributable to prescription opioids and unspecified drugs. These differences by age, sex, and type of drug have generally become more apparent in recent years.

The description of the association between drug overdose deaths and race in the literature has been mostly limited to the reports that show

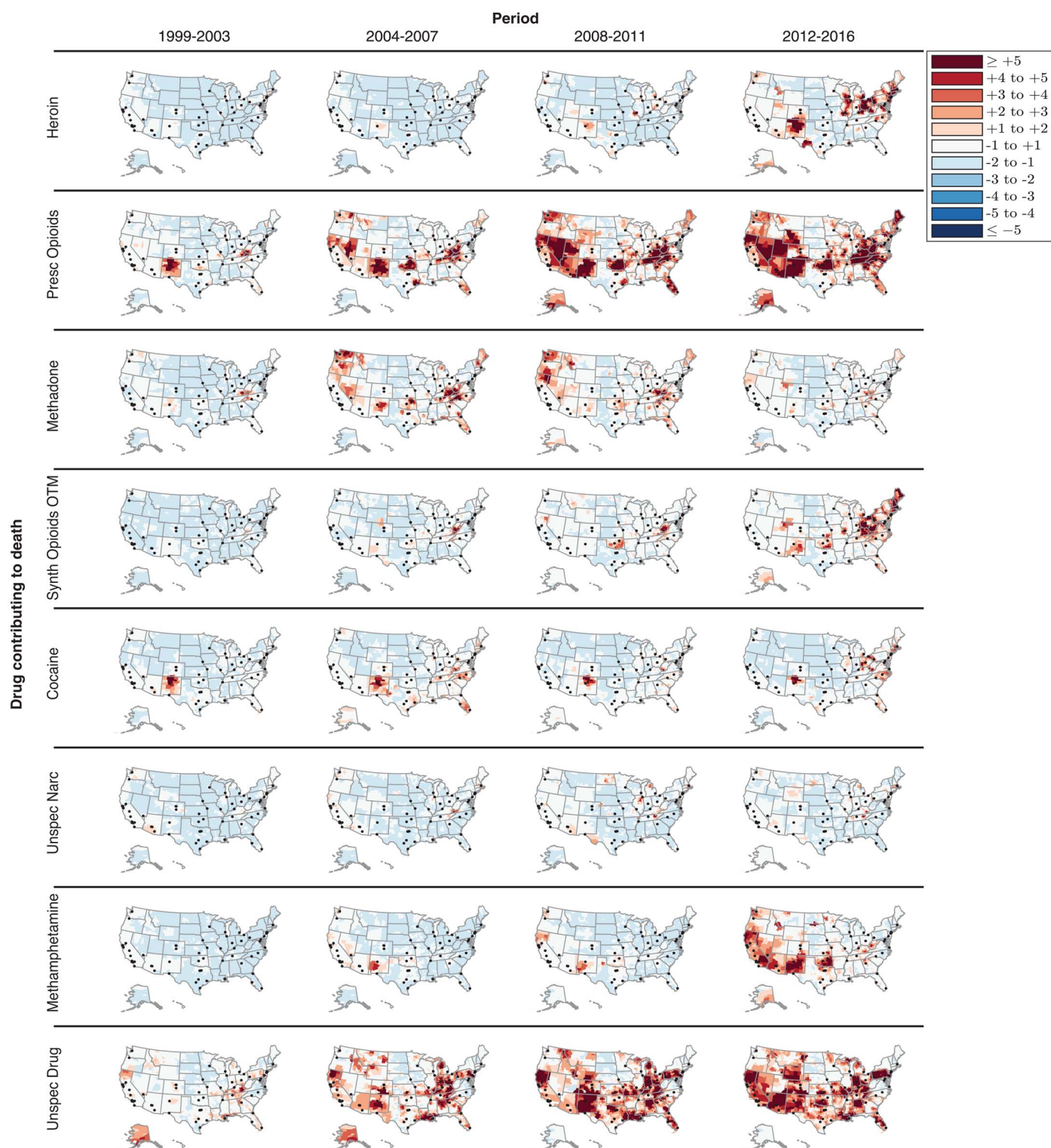
increased mortality rates, especially for opioids among whites (22–24, 29–31). In addition to the increased overdose deaths among whites, the heatmaps reveal that the age showing the peak mortality rate for cocaine among blacks has increased with each year, indicating a cohort aging effect. This pattern is especially noticeable among men and in urban counties. Among whites, the younger age group is at greatest risk for heroin and synthetic opioid deaths, whereas among blacks, the older age group is at greater risk.

The increase in drug poisoning mortality in 2016 is due to increased mortality from multiple drug-specific subepidemics: synthetic opioids (most likely fentanyl) among males, whites, and those in urban counties; heroin among young adults; prescription opioids among the middle-aged and blacks; and cocaine and methamphetamine among a wider age range, males, and whites.

To reveal geographic hotspots of each of the drugs over time, we also performed geospatial hotspot analyses of deaths due to each drug, broken into historical time intervals. Figure 3 shows the geographic distribution of eight drug classes at each of four periods. Taken together, these maps provide a synoptic view of changing landscape of drug mortality hotspots. [See the supplementary materials for a detailed description of the methodology.]

From 1999 to 2016, the epidemic intensity, as well as the spatial distribution of deaths attributed to prescription drugs, heroin, synthetic opioids other than methadone, cocaine, and methamphetamine, have all increased. Only for methadone has the epidemic intensity and spatial distribution peaked and then declined. Although the overall national epidemic may be smooth and continuous, each drug has shown a specific geospatial pattern of spread during this 18-year period. Heroin hotspots have changed from being closely clustered around large cities to being distributed more widely, especially in the Northeast and the Southwest. Prescription opioid hotspots initially were prominent in the southwestern United States and Appalachia but subsequently spread to involve much of the western United States, Oklahoma, Florida, and New England. Fentanyl and fentanyl analog hotspots have centered in opioid hotspots, especially in the Appalachian and Northeast regions. Cocaine hotspots have also centered around large cities but have diffused more broadly in recent years. Methamphetamine deaths have increased most dramatically in the western and southwestern United States. Almost every region in the country is a hotspot for mortality from one or more drugs. The only large region that appears to have been relatively spared (a relative “cold spot” for all drugs) is composed of the north central states.

These detailed demographic and geographic analyses do not suggest obvious mechanisms as to how multiple drug-specific subepidemics have merged into a single smooth exponential 38+ year process. Indeed, these findings add to the paradox by revealing how disparate the individual drug epidemics are.



**Fig. 3. Geospatial hotspot analysis by drug and period.** The  $G_i^*$  statistics are standardized using pooled statistics across all drugs and periods. The various shades of red and blue indicate pooled standard deviations above and below the pooled mean, respectively, as shown in the legend. The small black

circles indicate major cities with populations greater than 300,000 people. None of the regions were less than 2 pooled standard deviations below the pooled average. (Synth Opioids OTM: synthetic opioids other than methadone. This category includes fentanyl and its analogs.)

Effective public health responses will be crucial to address the USA drug crisis. Understanding the demographic and geographic characteristics of the subepidemics as reflected by overdose death patterns may be valuable in designing and strengthening “upstream” public health surveillance systems for substance abuse and non-fatal overdoses among living persons (32), and elucidation of the underlying complexity of the drug-specific subepidemics may facilitate development of more effective, locally tailored primary, secondary, and tertiary prevention strategies (33, 34). For the large existing population of persons with substance use disorder or addiction (35), availability of and access to treatments and harm reduction services that are subepidemic specific may be valuable in preventing more overdose deaths. Lastly, better understanding of local drug death patterns may lead to innovative collaborations between public health and law enforcement, which could include data sharing (36), partnership at the local and community level on harm reduction, and linking people with addiction to treatment (37).

### Caveats

Our findings should be interpreted with caution. First, there is substantial variation in the level of specificity of drug reporting for vital statistics across states and/or counties. A recent analysis found that in 2015, the percentage of overdose deaths with the drug unspecified ranged from 0% in the District of Columbia to just over 50% in Pennsylvania (38). The geographic distribution of these deaths not attributed to specified drugs can be seen in Fig. 3. This analysis and others (39) have found that states with centralized medico-legal systems have more complete drug reporting than states with decentralized systems. Figure S1 reproduces Fig. 2 with data only from states that produce good-quality data [as defined by the U.S. Centers for Disease Control and Prevention (CDC)] with fewer unspecified drug overdose diagnoses, and the results are almost identical, supporting the validity of the national-level data analyses.

Second, our categories of specific drug mortality rates are not mutually exclusive; therefore, overdose deaths that involve multiple drugs could be counted more than once. Multidrug abuse and overdose are increasing, and it is not always clear which drug or drugs are responsible for the overdose. Figure S2 shows how the relationships among various drugs have changed over time. In this figure, we show that the percentage of death certificates listing synthetic opioids OTM (other than methadone), cocaine, and methamphetamine as a secondary drug has increased dramatically in recent years, regardless of the index drug. While, the percentage of deaths attributed to heroin in addition to another drug is showing early signs of decline, this decline is, of course, only relative to the rapid rise in deaths due to the index drug. Additionally, the 10th revision of the International Classification of Diseases (ICD-10) only has a set number of codes for drug classes. Overdoses are

now being attributed to new drugs, such as fentanyl analogs, but the drug class codes have not changed (e.g., acyl fentanyl would be coded as T40.4), meaning that even with complete drug reporting, death certificates lose some drug specificity during the coding process. Additionally, coroners and medical examiners may not be able to identify newer psychoactive substances, indicating that these drugs will not be recorded on the death certificate. Such ambiguities in diagnostics do not affect our main finding of an exponential increase in the rate for overall drug overdose, as each overdose death is counted once.

Third, the intent of an overdose death is not always easy to determine by a medical examiner or coroner. Our study only focused on unintentional or accidental drug overdoses, which constitute roughly 85% of all drug overdoses every year; however, we recognize that the practice or capacity of determining intent varies by states.

Lastly, the dynamics of the substance use epidemic are not fully captured in drug overdose mortality data alone. A more complete analysis would also describe the initiation, natural history, treatment, and progression of drug use.

### The opioid crisis may be part of a larger, longer-term process

The epidemic of drug overdoses in the United States has been inexorably tracking along an exponential growth curve since at least 1979, well before the surge in opioid prescribing in the mid-1990s. Although there have been transient periods of minor acceleration or deceleration, the overall drug overdose mortality rate has regularly returned to the exponential growth curve. This historical pattern of predictable growth for at least 38 years strongly suggests that the epidemic will continue along this path for several more years. By contrast, the recent historical variability with which some specific drugs have waxed and waned makes predictions about the future role of specific drugs far more uncertain. Indeed, it is possible that in the future, the drug overdose epidemic may be driven by a new or heretofore obscure psychoactive substance.

Understanding the forces that are holding multiple subepidemics together into a smooth exponential trajectory may be important in revealing the root causes of the epidemic, and this understanding may be crucial to implementation of prevention and intervention strategies. Economic and technological “push” factors may be at work to increase supply, such as improved communications and supply chains, efficiencies in drug manufacturing, and expanding drug markets, leading to lower prices and higher drug purities (40, 41). Sociological and psychological “pull” forces may be operative to accelerate demand, such as despair, loss of purpose, and dissolution of communities (42, 43). Elucidation of the dynamics of the “deep” drivers of the overdose epidemic may provide valuable new insights.

### Materials and methods

This section provides a summary of the materials and methods. A more detailed explanation

can be found in the supplementary materials. Death information was obtained from the Mortality Multiple Cause Micro-data Files from 1979 to 2016. These data use ICD-9, enabling us to identify accidental drug poisoning deaths since 1979. In addition, we can identify specific drugs as contributory causes of accidental overdose deaths since 1999, because the use of ICD-10 starts from this time. For example, the ICD-10 code for heroin is T40.1, and for natural and semi-synthetic opioids (including prescription opioids), the code is T40.2.

To illustrate the changing dynamics of the drug-overdose deaths on multiple levels, we examined overdose mortality rates at three levels of detail: (i) national level, by drug, over time; (ii) national level, by drug, over time, with detailed analysis by demographic groups of age, sex, race, and urbanicity; and (iii) county-level cluster analysis, by drug, over time (hotspot analysis).

For national-level analyses, we computed mortality rates for individuals by drug codes and by age, sex, race, and urbanicity. For each computation, we used the appropriate denominator from the U.S. census population estimates from 1999 through 2016. To distinguish rural from urban counties, we used the 2013 Rural-Urban Continuum Codes (RUCC). RUCC codes 1–3 were considered urban, and RUCC codes 4–9 were classified as rural.

In the county-level analysis, we used the Getis-Ord  $G_i^*$  statistic to show geospatial clustering of hot (high) and cold (low) spots of mortality rates. The  $G_i^*$  statistic identifies these hot and cold spots on the basis of contiguous counties. The  $G_i^*$  statistic is essentially a Z-score standardized by a mean and standard deviation of mortality rates in all the counties. Typically, the  $G_i^*$  statistic can display geospatial information on one dimension such as mortality rates. To add additional dimensions and compare mortality rates by drug and time, we restandardized the  $G_i^*$  statistics by using the pooled mean and standard deviations of the  $G_i^*$  statistics across all drugs and over time. This restandardization allowed us to produce a set of comparable maps across time and drugs.

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# Science

## Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016

Hawre Jalal, Jeanine M. Buchanich, Mark S. Roberts, Lauren C. Balmert, Kun Zhang and Donald S. Burke

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### Analyzing the drug abuse epidemic

There is a developing drug epidemic in the United States. Jalal *et al.* analyzed nearly 600,000 unintentional drug overdoses over a 38-year period. Although the overall mortality rate closely followed an exponential growth curve, the pattern itself is a composite of several underlying subepidemics of different drugs. Geographic hotspots have developed over time, as well as drug-specific demographic differences.

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